also evaluated the relationship between culture positivity, IA, and clinical outcomes.

Methods: A retrospective cohort of THA/TKA PJIs, from 2009 to 2016, were identified by ICD codes, and confirmed by chart review. IA diagnosis was also confirmed by use of IA-specific medications. CN cases were defined as PJIs with no evidence of microbial growth in intraoperative cultures and CP PJI cases were defined by positive microbial growth in intraoperative cultures. Treatment failure was defined as subsequent surgical treatment for infection after the initial infection surgery. H&E slides of OA and IA PJI cases matched by age (+/-5) sex, and culture status were reviewed by a pathologist for evidence of the histopathologic features listed in Table 2. Fisher's exact test, chi-square test, and Kaplan-Meier estimates were used.

Results: 807 PJI cases were identified including 36 IA (33 RA and 3 SLE) and 771 OA. A higher proportion of IA PJI were CN (N=10, 27%) vs. OA PJI (N=109, 14%, $p=0.02$). IA-PJI were younger, female, on glucocorticoids, and with more comorbidities. Type of surgical treatment did not differ significantly between IA and OA groups. Comparing CN-IA vs. CP-IA, no difference was observed in age, smoking, diabetes, surgical treatment, IA-specific meds or Charlson comorbidities. One-year survivorship of CN-IA and CN-OA were 66% and 87% ($p>0.05$). Across all CP cases, 57% were staphylococcal, with no differences between groups. Treatment failure was more frequent for CP-IA (42%) compared to CP-OA (30%), ($p=0.2$).

Histopathology of 88 PJIs (31 IA and 57 OA) was reviewed. The IA cohort presented with more chronic inflammation ($p=0.001$) than the OA cohort. Within the IA cohort, a higher proportion of CP-IA had >10 PMN per HPF ($p=0.003$) and met MSIS criteria ($p=0.009$). Comparing CP-OA and CN-OA, there were no significant differences in histopathology findings or number of patients meeting MSIS criteria.

Conclusion: IA PJIs are more likely to be culture negative than OA PJIs. Although our analysis was limited by our cohort size, our findings including differences in histopathology, and better clinical outcomes suggest the presence of biologic differences between CN and CP PJI that require further study.

TABLE 1. Patient characteristics in IA and OA PJIs

	IA		OA		p-value
	N	%/SD	N	%/SD	
Total	36		771		
Age	58.5	11.4	66.8	12	<.001
BMI	30.2	6.7	30	6.7	0.861
Female	28	77.8	332	43.1	<.001
CCI	2.8	1.7	1.7	2.1	0.002
Smoking	4	11.1	86	11.2	0.792
Glucocorticoids	10	27.8	39	5.1	<.001
Culture Negative	10	27.8	109	14.1	0.024
Treatment Success at 2 years	19	52.8	509	66	0.146

IA - inflammatory arthritis; OA - osteoarthritis; PJI - prosthetic joint infection; CCI - Charlson Comorbidity Index

TABLE 2. Histopathology and clinical presentation in IA and OA PJIs

	OA (N=57)		CP-IA (N=23)		CN-IA (N=8)	
	N (%)	p-value	N (%)	p-value	N (%)	p-value
Pathology Review						
>10 PMN per HPF	42 (74)	0.806	20 (87)		2 (25)	0.003
Chronic Inflammation	13 (23)	0.001	18 (78)		5 (63)	0.393
Necrosis	17 (30)	1	8 (35)		1 (13)	0.38
Clinical Presentation						
MSIS	50 (88)	0.747	22 (96)		4 (50)	0.009
Sinus Tract	7 (12)	0.233	5 (22)		2 (25)	1
Elevated ESR or CRP	41 (72)	0.622	17 (74)		7 (88)	1
Elevated Synovial WBC	33 (58)	0.823	13 (57)		6 (75)	1
Elevated Synovial %PMN	31 (54)	0.377	14 (61)		6 (75)	0.333

OA - osteoarthritis; IA - inflammatory arthritis; CP - culture positive; CN - culture negative; MSIS - meets Musculoskeletal Infection Society diagnostic criteria

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FRI0404

SEPERATION OF HIGH AND LOW RESPONSE GROUPS IN OSTEOARTHRITIS USING SERUM CARTILAGE DEGRADATION AND FORMATION MARKERS – A 3 YEAR FOLLOW-UP ON THE FORWARD STUDY TESTING THE EFFICACY OF SPRIFERMIN

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Background: In osteoarthritis (OA), response to different interventions could be more pronounced in different endotypes of cartilage turnover. Data from UK biobank suggest that an endotype of low cartilage repair is associated with structural progression in osteoarthritis (OA)[1]. Sprifermin a truncated and recombinant FGF18 have been shown to induce chondrocyte proliferation and cartilage formation in vitro settings[2–4]. Efficacy on cartilage thickness in OA was recently demonstrated in the FORWARD study[5].

Objectives: We investigated markers of cartilage formation (serum PRO-C2) and degradation (urine CTX-II), to assess profiles indicative of chondrocyte metabolic activity would be associated with both structural and symptomatic responses to sprifermin.

Methods: Serum and urine from participants of the FORWARD study, a phase II clinical trial testing the efficacy of intra-articular (IA) sprifermin, were collected throughout the study. Clinical data recorded at baseline, year 2 and year 3 follow-up were used, including cartilage thickness and WOMAC. All available baseline samples of the placebo and treatment arms were assessed for serum PRO-C2 and urinary CTX-II. Patients were separated into dichotomized groups based on 33, 50 or 66 percentiles cut-points and two-year treatment responses were compared in a prospective-retrospective statistical design manner.

Results: Patients with low baseline PRO-C2 (<66%), in the 100ug/4x treatment arm, had greater difference to placebo in cartilage thickness as compared to the high PRO-C2 and all-comers groups (0.06 vs 0.03 and 0.05 mm, respectively) at two and three years (Fig.). Similar effect was seen for low CTX-II (<50%) (0.07 vs -0.03 and 0.05 mm, respectively). In addition, the WOMAC placebo effect was reduced in the low PRO-C2 and the low CTX-II groups, resulting in a difference compared to placebo of -0.81 vs. 1.35 (low vs high proC2 and -2.35 vs 1.47 (low vs high CTX-II)).

Conclusion: We noticed that low baseline PRO-C2 and CTX-II indicative for low metabolic activity of chondrocytes were associated with improved symptomatic outcome and slightly increased cartilage thickness compared to high metabolic activity. The parallelism between PRO-C2 and CTX-II point towards the existence of a low cartilage repair endotype and might reflect a subgroup of patients with higher sensitivity towards interventions - an effect that was maintained over three years.

Fig. 1: Longitudinal change in cartilage thickness (mm) in the total femorotibial joint in patients with low and high levels of PRO-C2 (top panel) and CTX-II (lower panel). Data are shown as mean with 95% CI of absolute change from baseline up to 3 Years.

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FRI0405

CARTILAGE BIOMARKERS S-COLL2-1 AND S-COLL2-1NO2 ARE HELPFUL IN IDENTIFYING KNEE OSTEOARTHRITIS PATIENTS AT RISK OF DISEASE WORSENING

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Background: Coll2-1 is a peptide of 9 amino acid located in the triple helix of type II collagen molecule reflecting cartilage degradation (1). Coll2-1NO2 is the nitrated form of Coll2-1 and considered as a biomarker of the inflammatory-related cartilage degradation (2). This peptide is involved in osteoarthritis physiopathology since it was demonstrated that Coll2-1 induced synovitis in rat.

Objectives: To identify if biochemical markers s-Coll2-1 and s-Coll2-1NO2 are associated to knee osteoarthritis (OA), focusing on pain, function as well as structural features assessed by MRI in various knee compartments and to assess their ability at predicting knee OA worsening.

Methods: 116 subjects with knee OA were followed during one year with pain, function and MRI evaluation (PRODIGE study, NCT02070224). Type II collagen-specific biomarker Coll2-1 and its nitrated form Coll2-1NO2 were directly measured in serum using immunoassays at baseline and after three, six and twelve months follow-up.

Results: sColl2-1 and sColl2-1NO2 were associated to several baseline knee features quantified with Whole-Organ Magnetic Resonance Imaging Score (WORMS). S-Coll2-1 was significantly correlated with bursitis ($r=0.29$, $P<0.01$), bone attrition ($r=0.25$, $P=0.01$), cysts ($r=0.24$, $P=0.02$) and cartilage ($r=0.23$, $P=0.03$) WORMS sub-scores for the whole joint as well as with the medial femorotibial joint sum score ($r=0.26$, $P=0.01$) and medial femorotibial joint cartilage ($r=0.23$, $P=0.02$). s-Coll2-1NO2 was correlated with WORMS total score ($r=0.23$, $P=0.02$), WORMS scores in the patellofemoral ($r=0.23$, $P=0.02$) and medial femorotibial compartments ($r=0.21$, $P=0.03$) and with osteophytes scores ($r=0.27$, $P<0.01$). Baseline s-Coll2-1NO2 was higher in subjects with a pain worsening (426.4 pg/mL [278.04-566.95]) as compared to non-progressors (306.84 [200.37-427.84]) over one year (AUC=0.655, $P=0.015$).

Conclusion: Cartilage biomarkers s-Coll2-1 and s-Coll2-1NO2 are associated to several knee OA features quantified with WORMS scoring system on MRI. Serum values of Coll2-1NO2 are also associated to a worsening of target knee pain over one year. Coll2-1 and Coll2-1NO2, in association with other structural features, pain and function, could help at identifying OA phenotypes and patients at risk of OA worsening.

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FRI0406

CARTILAGE REPAIR ACTIVITY DURING JOINT-PRESERVING TREATMENT MAY BE ACCOMPANIED BY OSTEOPHYTE FORMATION

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Background: Knee joint distraction (KJD) is a joint-preserving treatment to postpone total knee arthroplasty (TKA) and has shown cartilage repair and clinical improvement in patients with severe knee osteoarthritis (OA), as has high tibial osteotomy (HTO). The observed cartilage repair activity could be related to an increase in transforming growth factor- β 1 (TGF β -1), which increases in the synovial fluid (SF) during KJD treatment.¹ However, animal and ex vivo human studies have shown that TGF β -1 also induce formation of osteophytes, generally seen as an OA severity hallmark. Similarly, interleukin-6 (IL-6) was observed to increase in SF during KJD treatment and may also be associated with osteophytosis.

As such, we hypothesized that joint-preserving regenerative treatments demonstrating cartilage repair activity lead to general tissue (re)generation, including osteophytosis.

Objectives: To analyze osteophytosis after KJD and compare this to HTO and natural progression in knee OA.

Methods: 63 KJD patients were included in several clinical trials, one of which was a randomized controlled trial comparing patients indicated for HTO, but treated with KJD (KJD_{HTO}; n=23) vs. patients treated with HTO (n=46). All patients received standardized radiographs before and one and two years after treatment, used to measure osteophyte size. Only patients with measurements at baseline and two-year follow-up were included. As a control group for natural progression, untreated knee OA patients from Cohort Hip & Cohort Knee (CHECK; n=1002) were studied. Only patients who received a TKA during follow-up were included, using their last two measurements before treatment to reflect natural two-year progression (n=44).

A separate group of 20 patients treated with KJD in regular care underwent SF aspirations before and after treatment, and TGF β -1 and IL-6 levels were measured by immunoassay (Mesoscale Discovery). Unstandardized radiographs were acquired before and one year after treatment, used to score osteophytes with the revised Altman score, resulting in a 0 (normal) to 12 (severe) whole-joint score. Only patients with radiographs and SF aspirations at both baseline and one-year follow-up were included.

Results: After two years, both KJD (n=58) and HTO (n=38) patients showed a significant increase in osteophyte size (+6.2mm² and +7.0mm² resp.; both $p<0.003$; figure 1), with no significant differences between the treatments ($p>0.38$). Untreated CHECK patients who underwent TKA did not show significant two-year osteophyte changes before treatment (+2.1mm²; $p=0.207$; figure 1) and showed significant differences compared with KJD and HTO groups (both $p<0.044$). In the KJD SF aspiration group (n=17), the Altman osteophyte score was not different at one year compared to baseline (+0.2 points; $p=0.653$) and there was no association between baseline biomarker values and the baseline Altman osteophyte score, or between changes in these parameters (all $p\geq 0.28$). Trichotomization of patients in groups with a decrease, no change or increase in total Altman osteophyte score indicated that there was a statistically significant difference between the three groups in changes in TGF β -1 ($p=0.044$; figure 2A), but not IL-6 ($p=0.898$; figure 2B).

Conclusion: After KJD treatment, joint space widening and clinical improvement are accompanied by osteophytosis. Similar results were observed after treatment with HTO, suggesting effects occur in regenerative joint-preserving